TOBACCO INDUSTRY RESEARCH COMMITTEE (#225 CF #128
Activated 7/1/56
150 East Forty Second Street Renewed 7/1/57
" 7/1/58)
New York 17, N.Y.

Application For Research Grant

Date: December 19, 1958

1. Name of Investigator: Herbert McKennis, Jr., Ph. D.

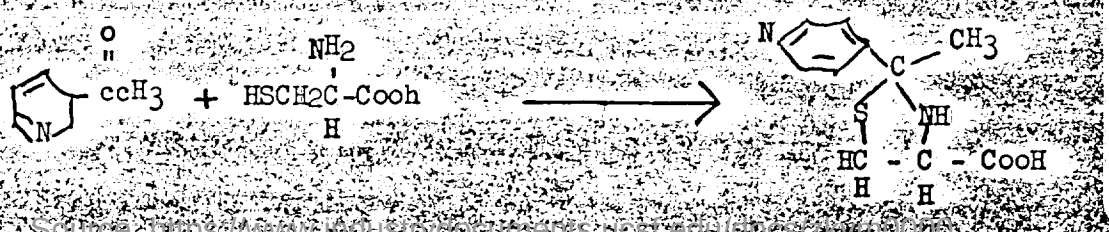
2. Title: Professor of Pharmacology

3. Institution & Address: Medical College of Virginia
Richmond 19, Virginia

4. Project or Subject: Metabolism of Antinicotinic Acid Compounds of Tobacco Smoke

5. Detailed Plan of Procedure (Use reverse side if additional space is needed):
In addition to nicotine tobacco smoke contains a variety of pyridine compounds including cotinine and acetylpyridine (Quinn, Twelfth Tobacco Chemists' Research Conference). Current studies in this laboratory have done much to establish that the nicotine metabolite cotinine is remarkably devoid of gross physiological effects in comparison with the parent compound nicotine. Recent work in other laboratories has tended to implicate nicotinic acid deficiency as a causative factor in experimental cancer. 3-Acetylpyridine already has assumed an important role as an experimental antagonist of nicotinic acid. In addition it has been observed that extensive brain damage arises (Hicks, Am. J. Pathol. 31, 189 (1955); Coggeshall and MacLean, Proc. Soc. Exp. Biol. Med. 98, (1958) ). If it is assumed that the deleterious effects arise from 3-acetylpyridine itself or a condensation product in the form of pyridine nucleotides, it is interesting to contemplate the possibility that small amounts of 3-acetylpyridine, such as are present in smoke, are metabolized to compounds which do not in themselves possess the physiological actions of 3-acetylpyridine.

Preliminary experiments (unpublished from this laboratory) have shown that 3-acetylpyridine is metabolized by the dog to a minimum of at least 4 Koenig positive components. These have been separated by chromatographic methods but not in sufficient quantity for chemical identification and physiological studies. Preliminary evidence also indicates that 3-acetylpyridine will react with cysteine to form a thiazolidine:



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It is proposed to administer 3-acetylpyridine and isolate by chromatographic techniques sufficient quantities for structural determinations and subsequent synthesis in quantities sufficient for biochemical studies. Compounds arising from the metabolism of 3-acetylpyridine which do not give the Koenig reaction can by fractionated by means of a $C^{14}$ label (obtained from $C^{14}$ nicotinic acid which is available for the synthesis of 3-acetylpyridine).

6. Budget Plan:

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|---|---|
| Social Security | $ 240 |
| Salaries | $ 11,000 |
| Expendable Supplies | $ 4,500 |
| Permanent Equipment | $ 3,000 |
| Overhead (10%) | $ 1,939 |
| Other (Travel) | $ 650 |
| Total | $ 21,329 |

7. Anticipated Duration of Work: Three years.

8. Facilities and Staff Available: General pharmacologic and biochemical equipment, Warburg apparatus, greenhouse for growing $C^{14}$ labelled pyridine compounds, Carey recording spectrophotometer, $C^{14}$ counting equipment.

9. Additional Requirements: What, if any, will depend upon how the product develops.

10. Additional Information (Including relation of work to other projects and other sources of supply): Staff to be hired: Ph.D. full time, $8,000, technician, $3,000. Part-time will include Dr. Herbert McKennis, Jr. and Edward S. Bowman, Public Health Research Fellow. Other personnel with experience in pyridine compounds will be available for consultation as required.

The breakdown on equipment is:

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|---|---|
| pH Meter | $ 500 |
| Deep Freeze | $ 500 |
| Ice box | $ 400 |
| Part cost of infrared equipment | $ 1,600 |
| | $ 3,000 |

/s./ Herbert McKennis, Jr.
Director of Project

/s./ B. B. Smith
Business Officer of the Institution

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